Relationship Between Plasma Levels of Prolactin and the Severity of Negative Symptoms in Patients with Schizophrenia

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ABSTRACT:
Relationship between plasma levels of prolactin and the severity of negative symptoms in patients with schizophrenia

Objective: The aim of this study was to evaluate the relationship between plasma levels of prolactin and negative symptoms.
Methods: One hundred fourteen patients with schizophrenia were included in this cross-sectional study. The patients were classified into groups with and without hyperprolactinemia. Plasma levels of prolactin and clinical features were compared between these groups.
Results: Negative symptom scores in the group with hyperprolactinemia were significantly higher than in the non-hyperprolactinemic group. There was also a positive correlation between plasma levels of prolactin and negative symptom scores. However, there was no statistically significant difference between schizophrenia subtypes with regard to plasma prolactin levels. Patients treated with conventional neuroleptics or novel antipsychotics such as risperidone, paliperidone and amisulpride had higher prolactin levels than patients treated with aripiprazole, olanzapine, quetiapine, ziprasidone, and clozapine.
Conclusion: This study indicated that we should be aware of prolactin levels, especially when negative symptoms are prominent in patients with schizophrenia. Plasma levels of prolactin could be an important biological marker for the severity of negative symptoms in the treatment of patients with schizophrenia. Thus, this finding may change the present pharmacotherapy for negative symptoms in schizophrenia based on prolactin levels.

Keywords: schizophrenia, negative symptoms, prolactin, antipsychotic

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INTRODUCTION

Schizophrenia is a severe psychiatric disorder, with an onset usually in early adulthood, which causes extensive disability in the affected patients. Animal and human studies indicate that sex steroids may have direct effects on brain functions. Therefore, gonadal steroids could play a significant role in the pathophysiology and course of schizophrenia[1-4]. Additionally, it has been described that hyperprolactinemia is associated with disturbances in the levels of key reproductive hormones including estrogen and testosterone. Prolactin is also a gonadal hormone that is valuable in monitoring the treatment of schizophrenia. Neuroendocrinological research suggests that a dysfunction of the hypothalamic–pituitary–adrenal and/or hypothalamic–pituitary–gonadotropin axis may contribute to the pathophysiology of schizophrenia[5,6]. It has been indicated that both estrogen and testosterone levels are associated with negative as well as

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positive behavioral, cognitive and affective symptoms. Although there is a paucity of research regarding the relationship between the plasma levels of reproductive hormones and negative symptoms in patients with schizophrenia, knowledge of the role of reproductive hormones in the pathophysiology of schizophrenia is still growing[7-10]. Negative symptoms have become a special research interest in the last decade because atypical antipsychotic drugs are claimed to have an improved therapeutic efficacy compared to older, typical agents used to control negative symptoms in schizophrenic patients[4,11].

Antipsychotics remain the cornerstone of treatment for patients with schizophrenia. Although the introduction of conventional antipsychotics more than half a century ago heralded a major advance in the treatment of schizophrenia, these compounds have serious limitations in terms of both efficacy and tolerability[11-13]. It is well established that neuroleptics have pronounced effects on hormone secretion, especially on the release of prolactin from the anterior pituitary gland, and decreased libido occurs in a considerable proportion of schizophrenic patients treated with traditional antipsychotics[14-22]. Conversely, new generations of atypical drugs have variable tendencies to induce hyperprolactinemia[23,24]. The production of prolactin is inhibited by dopamine release in the hypothalamic-pituitary circuit and can be elevated by blocking type 2 (D2) dopamine receptors. Most antipsychotic drugs can therefore cause increases in prolactin secretion[25]. Hyperprolactinemia is a frequent but often neglected side effect of typical, but also of many atypical antipsychotics such as amisulpiride and risperidone. In addition to galactorrhea, potential consequences are suppression of the hypothalamic-pituitary-gonadal axis with hypogonadism, sexual dysfunction, infertility, and also irregularities of the menstrual cycle in women. Potential long-term consequences are primarily osteopenia and osteoporosis with an enhanced risk of fractures. Additionally, sexual side effects may reduce adherence to medication in younger patients[26-29].

In addition, it is important to consider whether elevated prolactin is related to specific symptoms or subtypes of schizophrenia, which is a multidimensional entity. Some studies yield a clearer, though not completely understandable picture; there is a reasonably consistent negative association between plasma prolactin and substitute measures of positive symptoms—such as specific delusions or the paranoid subtype of schizophrenia. Some researchers have interpreted these results in terms of increased dopaminergic activity in patients with paranoid or positive symptoms, which is consistent with the dopamine hypothesis of schizophrenia[30-35]. The association of lower prolactin levels with positive symptoms and "paranoid" symptoms in particular is in line with the revised dopamine hypothesis of schizophrenia. This association can definitely be interpreted as suggesting increased dopamine transmission in this subgroup, with the same proviso as above, i.e. we do not know how well prolactin correlates with dopamine activity in the limbic pathway. If this finding can be replicated, it will provide some support for the concept of subtypes within the wide category of schizophrenia. The most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) has consciously removed the traditional subtypes[36], but finding a biomarker for a paranoid subtype could lead to a reversal of this change[37]. Conversely, Prasad et al. have reported higher prolactin levels in patients with positive symptoms[38]. In another study, Juchins et al. have reported there to be no relationship between prolactin levels and psychopathology[39]. An alternative interpretation remains confounded by the presence of studies with negative findings and by the variations in methodology adopted by different authors—particularly in terms of patient gender and measures used to assess symptom dimensions[37]. In addition, a few studies have reported a significant positive correlation between prolactin levels and negative symptoms[4,40].

Studies suggest that the relationship between prolactin levels and treatment response may be very important in the treatment of schizophrenic

patients. As prolactin increase is related to D2 receptor blockade, prolactin may be a useful representative marker of the blockade achieved and thereby—in an indirect manner—of the efficacy of antipsychotic drug medications. The results of the studies above suggest that there is a clear relationship between changes in prolactin levels and the response to some antipsychotics. It has been suggested that challenge tests can be used to assess the serotonergic effects of clozapine and that plasma prolactin can be used to estimate therapeutic doses of dopamine antagonists. These findings are both interesting but require replication. An increased prolactin response to fenfluramine was associated with treatment resistance in one study. Some of the most relevant positive results have been obtained in patients with schizophrenia suggesting that prolactin may be important as a biomarker of drug response[37].

Additionally, it has been reported that all antipsychotic side effects can have a persistant negative impact on patients' attitudes toward antipsychotic treatment and compliance[41,42]. Hyperprolactinemia, which may cause sexual dysfunction, can be highly distressing. Increased prolactin plasma levels, at the time of initial evaluation, were found to be associated with negative attitudes toward pharmacologic treatment[24]. However, this issue is overlooked in routine clinical examinations. Metabolic effects have dominated the literature for the last few years, but some studies show that hyperprolactinemia is not a benign condition. Many important questions about the effects of hyperprolactinemia still remain unanswered[25,43,44]. Many clinicians ignore the importance of hyperprolactinemia, especially in male patients. Therefore, it is extremely important to follow prolactin levels in patients with schizophrenia.

The aim of this study was to evaluate the relationship between plasma levels of prolactin and negative symptoms. It was also aimed at increasing the awareness of clinicians about prolactin levels in patients treated with antipsychotics.

METHODS

Subjects

This cross-sectional study was conducted in the Psychiatry Department of the GATA Haydarpasa Training Hospital in Istanbul, Turkey. One hundred and fourteen outpatients (95 males, 19 females) were included in the trial; subjects were included if they fulfilled DSM-IV criteria for schizophrenia established on the basis of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Patients were excluded from the study if they had a clinically significant organic, neurological disorder or showed mental retardation. All patients had no known endocrine disorders and were not receiving any hormone therapy. Plasma TSH and FT3 levels were in normal ranges. Patients could have been receiving antipsychotics for two months. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by an ethics committee at GATA Haydarpasa Training Hospital. Written informed consent was obtained before admitting subjects into the study. Cut-off points for the plasma prolactin levels were considered to be 19.4ng/ml in male patients and 26.5ng/ml in female patients. Non-significant differences were identified between patients with hyperprolactinemia and non-hyperprolactinemia with regard to basic demographic data including age, gender, substance use disorders and number of hospitalizations. Illness characteristics and demographic data were obtained from clinical interviews and medical records.

Hormone Assays

Blood samples were taken from individuals after 10-12 hours fasting. They were collected into tubes without any additives and were then centrifuged (4000 rpm/10 min). Serum samples were kept at -80°C. Measurement of serum prolactin, TSH, and T3 levels was performed by the Chemiluminescent Microparticle Immunoassay (CMIA) method using an Abbott i2000 Autoanalyzer (Abbott Diagnostics,

IL, USA). In addition, serum glucose, cholesterol, triglyceride, and HDL and LDL-cholesterol levels were measured by photometric methods, using an Abbott Architect c16000 Autoanalyzer (Abbott Diagnostics, USA).

Clinical Assessment

To evaluate positive and negative symptoms in patients with schizophrenia, as well as general psychopathology associated with schizophrenia, we used the 30-item Positive and Negative Syndrome Scale (PANSS)[45,46]. Each item is rated on a scale from 1 to 7. The sum of 30 items is defined as the PANSS total score and ranges from 30 to 210 points. The association between plasma levels of biochemical measurements and the severity of negative symptoms was evaluated according to the PANSS. The Barnes Akathisia Scale (BAS) is a rating scale that is administered by physicians to determine the severity of drug-induced akathisia. This scale includes objective and subjective items such as the level of the patient's discomfort. The BAS assesses the objective presence and frequency of akathisia, the level of an individual's subjective awareness and distress, and global severity. The objective rating is made using a four-point scale. The BAS subjective component consists of two items, both rated using four-point scales, i.e. Awareness of Discomfort and Distress Related to Discomfort. The BAS Global Clinical Assessment of Akathisia is rated using a six-point scale[47]. The Simpson Angus Scale (SAS) is composed of 10 items and used to determine pseudoparkinsonism. The severity of each item is rated using a five-point scale. SAS scores can range from 0 to 40. Signs assessed included gait, arm-dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation[48].

Statistical Analysis

Descriptive statistics were reported as frequencies and percentages for categorical variables and mean±standard deviation for continuous variables. Distribution of data was evaluated by using the One-Sample Kolmogorov-Smirnov test. Differences between the two groups were assessed by Student's t test. Correlations between clinical symptom scores and plasma prolactin levels were evaluated by the Pearson correlation test. Differences were considered to be significant when p values were lower than 0.05.

RESULTS

The study enrolled a total of 114 schizophrenic patients. All patients were divided into two groups, those with and without hyperprolactinemia, respectively. The average age of the hyperprolactinemic patients was 30.92±12.81 (n=61), while the non-hyperprolactinemic patients' (n=53) average age was 35.40±13.77 years. Hyperprolactinemia was detected in 53.7% of male patients (n=51) and 52.6% of female patients (n=10). Of the schizophrenic patients, 54.4% had no occupation, 13.2% were housewives, 17% were civil servants and 7% were workers. The monthly income of 53.5% of the patients (n=61) was 1000-2000TL. No significant differences were identified between patients with hyperprolactinemia and without hyperprolactinemia with regard to basic demographic data including age, gender, marital and educational status and plasma levels of lipids, thyroid hormones and glucose. Other comparisons of demographic features and biochemical measurements between groups are shown in Table 1.

According to the comparison of plasma prolactin levels and clinical features between groups, there was a statistically significant difference in the negative subscale scores of the PANSS (p=0.041). There was no statistically significant difference in plasma prolactin levels between the paranoid group and other types of schizophrenia. Additionally, patients with hyperprolactinemia had a lower weight than those in the other group (p=0.023). There was no statistically significant difference in the other clinical features between groups (Table 2).

Table 1: Comparison of some demographic features and biochemical measurements between groups

Sample characteristics	Patients with hyperprolactinemia (n=61) Mean±SD or n (%)	Patients without hyperprolactinemia (n=53) Mean±SD or n (%)	t or Chi-square	p
Age (years)	30.92±12.81	35.40±13.77	-1.788	0.077*
Gender				0.933*
Male	51(53.7)	44(46.3)		
Female	10(52.6)	9(47.4)		
Educational status	11.21±3.63	12.09±3.06	-1.403	0.163**
Marital status				
Married	20(55.6)	16(44.4)		0.827*
Single	38(53.5)	33(46.5)		
Divorced/Widowed	3(42.9)	4(57.1)		
Total Cholesterol	189.80±43.96	198.96±49.2	-1.038	0.302**
TG	153.63±84.55	178.03±108.65	-1.315	0.192**
HDL	48.21±10.38	47.15±12.60	0.482	0.631**
LDL	115.63±48.38	117.70±37.94	-0.252	0.801**
T3	3.21±0.42	3.18±0.58	0.315	0.754**
TSH	1.75±0.80	1.92±1.07	-0.918	0.361**
Fasting blood glucose	88.64±9.53	92.36±10.86	-1.799	0.075**

Notes: *Chi-square Test, **Student's t test

Table 2: Comparison of plasma prolactin levels and clinical features between groups

	Patients with hyperprolactinemia Mean±SD or n (%) (n=61)	Patients without hyperprolactinemia mean±SD or n (%) (53)	t or Chi-square	p
Prolactin	75.47±48.82	9.59±4.94	10.477	0.000**
Weight	77.57±12.95	82.99±11.83	-2.312	0.023**
Height	172.30±7.53	173.04±7.83	-0.514	0.608**
PANSS T	72.88±15.43	68.17±20.11	1.379	0.171**
PANSS P	16.49±4.44	16.70±5.25	-0.223	0.824**
PANSS N	21.92±5.98	19.19±7.72	2.070	0.041**
Age at onset (years)	26.30±8.54	23.87±5.61	1.813	0.073**
DUP (months)	12.49±18.45	10.19±21.34	0.612	0.542**
BAS	1.88±3.16	2.31±3.27	-0.702	0.484**
SAS	1.30±1.89	1.68±2.97	-0.780	0.437**
Family History				
Yes	15(44.1)	19(55.9)		
No	46 (57.5)	34(42.5)		0.190*
Suicide attempt				
Yes	8(38.1)	13(61.9)		0.117*
No	53(57)	40(43)		
Subtypes of Sch				
Disorganized	12(60)	8(40)		
Paranoid	38(48.7)	40(51.3)		0.204*
Residual	5(83.3)	1(16.7)		
ECT History				
Yes	11(55)	9(45)		0.933*
No	50(53.2)	44(46.8)		
Smoking and SUD				
Smoking	32(54.2)	27(45.8)		0.330*
Cannabis	8(66.7)	4(33.3)		
Inhalants	2(100)	0(0)		
No	19(46.3)	22(53.7)		

PANSS T: Positive and Negative Symptom Scale Total Score, PANSS P: Positive and Negative Symptom Scale Positive Score, PANSS N: Positive and Negative Symptom Scale Negative Score, SAS: Simpson Angus Scale, BAS: Barnes Akathisia Rating Scale, DUP: Duration of Untreated Psychosis, ECT: Electroconvulsive Therapy, SUD: Substance Use Disorder; Sch: schizophrenia.
Notes: *Chi-square test; **Student's t test

Table 3: Correlations between prolactin, T3, TSH and clinical measures in patients with schizophrenia						
	PANSS T	PANSS P	PANSS N	SAS	BAS	DUP
Prolactin	0.135	-0.040	0.201*	-0.081	-0.085	0.061
T3	-0.038	0.068	-0.010	0.120	0.146	-0.123
TSH	0.094	0.060	0.075	0.012	0.159	-0.102

PANSS T: Positive and Negative Symptom Scale Total Score, PANSS P: Positive and Negative Symptom Scale Positive Score, PANSS N: Positive and Negative Symptom Scale Negative Score, SAS: Simpson Angus Scale, BAS: Barnes Akathisia Rating Scale, DUP: Duration of Untreated Psychosis.
Notes: Spearman correlation, *p<0.05.

A significant positive correlation was detected between the negative subscale scores of the PANSS and plasma levels of prolactin in patients with schizophrenia. We did not find any significant correlation between the other clinical features and biochemical measurements. Other correlations are shown in Table 3.

Finally, patients were divided into two groups according to antipsychotic use. Group 1 consisted of patients who received conventional antipsychotics, risperidone, paliperidone or amisulpride (n=76). The other group (Group 2) consisted of patients who received olanzapine, quetiapine, aripiprazole, ziprasidone and clozapine (n=38). Plasma prolactin levels of the patients in group 1 (50.61±56.21) were higher than of patients in group 2 (18.50±26.14) (p=0.002).

DISCUSSION

The present study indicates that plasma levels of prolactin are positively correlated with the severity of negative symptoms in patients with schizophrenia. There was no statistically significant difference between the types of schizophrenia and plasma prolactin levels. Additionally, plasma prolactin levels of patients who received conventional antipsychotics, risperidone, paliperidone or amisulpride were higher than those of the other patients who received olanzapine, quetiapine, aripiprazole, ziprasidone and clozapine.

Negative symptoms play an important role in schizophrenia and are related to deficits in global functioning[4,13]. Abnormalities in the hypothalamic–pituitary–gonadal axis function have been reported in schizophrenic patients[2]. A review of the literature on prolactin and schizophrenia suggests that the relationship between them is complex and not limited to the adverse effects of antipsychotics. Studies in this area may lead to an improved understanding of schizophrenia, as well as a better definition of the effects of prolactin on social behavior and cognition in humans[37]. However, this study focused on hyperprolactinemia caused by antipsychotics and the relationship between clinical features.

Hyperprolactinemia is one of the most common side effects associated with antipsychotics and occurs in 40-50% of subjects[49]. The clinical consequences of prolonged hyperprolactinemia in males include sexual dysfunctions (such as diminished libido, orgasm problems, impotence) and other psychiatric symptoms like depression, memory deficits, and worsened psychosis[20]. The question to be considered is whether elevated prolactin levels are related to specific symptoms or subtypes of schizophrenia, which is a multidimensional entity. Low testosterone and high prolactin levels have been reported in male patients with schizophrenia, and it was noted that prolactin levels were positively correlated with the severity of negative symptoms[6]. However, the prolactin levels did not show any significant correlation with other hormone levels and severity of negative symptoms in another study[24]. Our results indicate that prolactin levels are associated with negative symptoms in patients with schizophrenia. The results of this study suggest that prolactin and hypothalamic–pituitary–gonadotropin axis functioning could play an important role in the negative symptoms of

schizophrenia. These results are in agreement with previous studies reporting the relationship between gonadal hormones and negative symptoms[4,7,9,40]. In addition, positive correlations have been reported between the prolactin response to a serotonergic challenge and negative symptoms[50] and between prolactin release after TRH administration and thought disorder[51]. We did not find any clinically significant correlations between the severity of symptoms evaluated by the PANSS subscales and T3 or TSH plasma levels. Likewise, negative correlations have been reported between prolactin response and severity of delusions[52]. Decreased prolactin responses have been associated with a "Kraepelinian" diagnosis of schizophrenia[53]. Conversely, another study found an association between lower basal prolactin levels and positive symptoms[54], which is consistent with the results of other studies[34,35]. The interpretation of these findings is complicated by many potential mechanisms that may be involved. The blunting prolactin response to dopamine antagonists[53,55,56] may indicate dopamine receptor supersensitivity. The worsening of positive symptoms[57] associated with a blunted response to serotonergic challenge may involve reduced serotonin receptor sensitivity. Conversely, exaggerated prolactin response to serotonin in resistant schizophrenia is indicative of serotonergic hyperfunction; this is consistent with the fact that clozapine, an antagonist at multiple serotonin receptors, is the treatment of choice in these patients[37]. However, there was no significant difference in plasma prolactin levels between paranoid schizophrenia and other subtypes of schizophrenia in our study.

There are gender differences in patients with schizophrenia and especially in negative symptoms of schizophrenia, which may be related to the action of the gonadal hormones[58]. Male patients with high prolactin plasma levels have been reported to have severe negative symptoms[4]. In our study, hyperprolactinemia was detected in 53.7% and 52.6%, respectively, of male and female patients receiving diverse antipsychotics. In some studies, hyperprolactinemia was detected in 40% of

male and 60% of female patients treated with conventional antipsychotic medications or risperidone[59]. There are two primary factors that may explain this finding: tolerance and the ceiling effect. However, no significant difference was identified between patients with hyperprolactinemia and non-hyperprolactinemia with regard to gender in our study. In addition to gender, diverse factors including sexual activity, stress, smoking, and drugs can affect the release of prolactin[25,60,61]. In this study, significant differences were not identified between hyperprolactinemics and non-hyperprolactinemics with regard to gender and smoking.

The atypical antipsychotic drug risperidone may produce substantially more severe effects of hyperprolactinemia than conventional agents. However, the majority of the other atypical antipsychotic agents (e.g. clozapine, olanzapine, quetiapine, ziprasidone) elicit significantly lower elevation of prolactin, most likely due to the lower dopamine D2 binding affinities[24,62,63]. Similar to literature reports in our study, plasma prolactin levels of patients who received conventional antipsychotics, risperidone, paliperidone or amisulpride were higher than those of other patients who received olanzapine, quetiapine, aripiprazole, ziprasidone, or clozapine. Elevated prolactin levels may be detected shortly after the initiation of antipsychotic treatment and its effect may persist for a long time[24]. Prolactin and some antipsychotics themselves have a direct effect on the hypothalamic neurons controlling gonadotropin secretion[64]. It is well documented that both dopaminergic and serotonergic neuronal activities participate in the regulation of the pituitary-gonadal axis (PGA)[65], so one can expect that these antipsychotics (risperidone, paliperidone, conventional antipsychotics, amisulpride) with high affinity for dopamine and serotonergic receptors affect plasma levels of PGA hormones[24,59]. The increase of prolactin levels may be a mechanism contributing to sexual problems along with weight gain, extrapyramidal symptoms and adrenergic, anticholinergic and serotonin antagonism[20]. Conversely, in our study the

patients without hyperprolactinemia had higher weights than patients with hyperprolactinemia. The cause of weight gain in these patients could be related to antipsychotics such as olanzapine, clozapine and quetiapine. Thus, weight gain in these patients was not associated with plasma prolactin levels in our study.

Antipsychotic-induced hyperprolactinemia is evident among patients with schizophrenia, and research suggests that elevations in prolactin levels may account for specific mental and physical health problems that are often observed in hyperprolactinemic patients. In particular, conventional antipsychotics and risperidone are consistently associated with 'prolactin-raising' effects, whereas other atypical antipsychotics are more likely to have 'prolactin-provent' properties. Certain antipsychotics have a lower potential for increasing prolactin levels, and this should be considered when prescribing an antipsychotic. Previous studies have shown that aripiprazole has a minimal effect on prolactin and is associated with lower prolactin levels when compared with other prolactin-provident antipsychotics. Current treatment options for antipsychotic-induced hyperprolactinemia include a decrease in antipsychotic dose or switching to a prolactin-provident medication. Further controlled studies and relevant guidance are essential to increase awareness and understanding of the impact of antipsychotic-induced hyperprolactinemia on mental and physical health in schizophrenia[49]. Thus, prolactin should be measured before starting a patient on a new antipsychotic. Essentially, the risk-to-benefit analysis should favor prolactin-sparing antipsychotics as a treatment alternatives[24,59]. Otherwise, before neuroleptic treatment is begun, and also at regular intervals there after, patients should be questioned about potential clinical signs of hyperprolactinemia. If clinical symptoms occur, switching to a prolactin-provident antipsychotic may be necessary. Generally hyperprolactinemia in schizophrenic patients should be taken into consideration much more seriously in a clinical approach[26].

The main limitation of this study was that the relationship between plasma levels of other gonadal steroids such as testosterone, FSH, or LH and the severity of negative symptoms seen in schizophrenia was not evaluated. In addition, female and smoking patients were not excluded. However, there was no relationship between plasma prolactin levels, gender differences and smoking. Additionally, it should be mentioned that the pathophysiological disturbances of schizophrenia may contribute to the disruption of the regulation of gonadal steroid hormone synthesis and release. However, this issue was not within the scope of this study. Another limitation was that the patients were not questioned about the sexual side effects caused by hyperprolactinemia.

CONCLUSION

This study indicates that we should assess prolactin levels when we detect negative symptoms in patients with schizophrenia. Clinicians should ask questions to detect hyperprolactinemia before starting treatment and during follow-up and should give patients relevant information. A decrease of the dose of antipsychotic medication (minimum effective dose) with caution might have a beneficial effect for patients with schizophrenia and negative symptoms. Alternatively, switching to a serotonin-dopamine antagonist drug (except risperidone, paliperidone, amisulpride) may be helpful since they cause less hyperprolactinemia than conventional antipsychotic drugs. In conclusion, this study indicates that the assessment of prolactin levels could be an important biological marker for the severity of negative symptoms in schizophrenia and these findings may change the present pharmacotherapy for negative symptoms based on prolactin levels of patients with schizophrenia.

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